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PEOPLE FOR THE ETHICAL TREATMENT OF ANIMALS

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RE: Docket Identification Number FDA–2012–D–0071

These comments on the Food and Drug Administration's (FDA) *Draft Guidance for Industry: Modified Risk Tobacco Product* [MRTP] *Applications* and the Institute of Medicine's (IOM) report, *Scientific Standards for Studies on Modified Risk Tobacco Products*, are submitted on behalf of People for the Ethical Treatment of Animals (PETA) and our more than three million members and supporters. PETA is committed to using the best available science to save animals from suffering in laboratory experiments and promote the acceptance of human-relevant methods for risk assessment.

We are very concerned that, in its current form, the draft guidance will lead to animal studies being conducted in support of MRTP applications. As IOM observes in its report, tobacco products are inherently hazardous, addictive products that are never truly safe or effective, and it is not possible to make laboratory animals use tobacco products the way humans do. While we appreciate FDA's efforts to hold tobacco manufacturers to a high standard, it is unconscionable that more animals be made to suffer and die in efforts to market some tobacco products as less harmful than others. Moreover, it is unacceptable that IOM advises requiring new animal studies, but fails to address minimizing animal use.

FDA must clearly state that no animal studies should be conducted in support of MRTP applications and remove all references to animal studies from its guidance. We recommend that evaluation of toxicity *in vitro* be completed and submitted and MRTP applications be made public prior to commencement of any further studies. In addition, we call upon FDA to meet with scientists from animal protection organizations in order to develop specific guidance to ensure that animals are not used in support of MRTP applications.

FDA Draft Guidance

As noted in the draft guidance, before an MRTP can be introduced into interstate commerce, an order from FDA under section 911(g) of the Food, Drug, and Cosmetic (FD&C) Act, as amended by the Family Smoking Prevention and Tobacco Control Act must be in effect with respect to the product. Section 911(g) establishes two bases for FDA to issue an order. FDA may issue a risk modification order only if it determines that the applicant has demonstrated that the product, as it is actually used by consumers, will significantly reduce harm to individual tobacco users as well as benefit the health of the population as a whole. If scientific evidence is not available for an application to meet the

standards for obtaining a risk modification order, FDA may instead issue an exposure modification order. In this case, FDA must find that the applicant has demonstrated that the scientific evidence that is available, without conducting long-term epidemiological studies, demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely.

While FDA does not explicitly recommend that animal studies be conducted in support of MRTP applications, *in vivo* studies are included among the types of nonclinical studies that it recommends to address the known clinical toxicities of tobacco products and evaluate the potential toxicities of the product as compared to other tobacco products. Specifically, FDA recommends that applicants seeking exposure modification orders submit nonclinical and/or human studies that demonstrate that the substance(s) or exposure(s) that have been reduced are harmful as well as nonclinical and/or human studies that demonstrate that use of the product is expected to result in a measurable and substantial reduction in morbidity or mortality to individual tobacco users. In addition, to address the effect on behavior among current tobacco users, FDA recommends that applicants submit nonclinical and/or human studies to assess the abuse liability and the potential for misuse of the product as compared to other tobacco products. Further, it is clear that FDA anticipates that animal studies will be conducted in support of MRTP applications, since it states that "[f]or *in vivo* animal studies, researchers should administer the test product to animals by a route representative of human exposure" and that "[a]n assessment of abuse liability may rely on a battery of studies that could include animal models of conditioned place preference, drug discrimination and self-administration."

IOM Report

In addition to comments on its draft guidance, FDA requests comments on IOM's recommendations, specifically Recommendation 2: ''The FDA should establish guidance that conveys an expected sequencing of studies, such that preclinical work is completed and submitted to the FDA before clinical (human subjects) work commences, and [FDA should establish] that there is a reasonable expectation based on preclinical work that a reduction or lack of harm will be seen in humans.''

IOM observes that the composition of tobacco and tobacco smoke has been the subject of intense study for at least the past 60 years leading FDA to develop a list of more than 100 harmful and potentially harmful constituents, the majority of which have been routinely analyzed and extensive data are available on their concentrations in tobacco and tobacco smoke. IOM concludes that laboratory analysis of constituents would be a standard first step in the initial evaluation of any new product. In addition, IOM notes that validated tobacco carcinogen and toxicant biomarkers are available and concludes that measurement of a panel of these biomarkers can provide a realistic assessment of human uptake of a variety of toxicants and carcinogens in tobacco products.

IOM identifies *in vitro* laboratory assays including the Ames test and tests on cytotoxicity, proliferation, and programmed cell death that provide routine toxicology

analyses. In addition, IOM identifies *in vitro* assays that address oxidative stress, inflammation, mucus production, and endothelial activation to be a standard step in evaluations of all tobacco products. These include assays to measure individual cytokines and a biphasic culture system for airway epithelial cells which reflects the *in vivo* situation allowing for cell activation and differentiation. While IOM recommends that evaluation of products *in vitro* should precede *in vivo* assays, it concludes that *in vitro* methods are not reliably quantitative to allow valid comparisons of substantially different tobacco products. IOM offers remarkably little advice on minimizing animal use, noting only that the number of animal studies required to characterize an MRTP preclinically could potentially be reduced by setting composition standards or limits for certain categories of MRTPs.

IOM correctly observes that it is not possible to make laboratory animals use tobacco products the way humans do and that there are inherent interspecies differences that prevent meaningful extrapolation of human effects. It notes that experiments with smokeless tobacco (ST) products and extracts conducted on hamsters, rats, and mice produce few tumors on an inconsistent basis and expresses concern that continual placement of ST will produce false positive results because of local irritation. With regard to combusted tobacco products, IOM notes that chronic bronchitis cannot be replicated in rodents and that the data are inconsistent as to whether inhaled tobacco smoke can induce tumors and cancers in animal models. **Nevertheless, despite these facts and the weight of similar evidence showing that results from animal studies are irrelevant to humans, IOM inexplicably recommends that animal studies be part of a complete battery of preclinical assays.**

IOM describes the role of preclinical assays as the identification of particularly risky or toxic products that should not be tested in humans as well as products that have reasonable potential to reduce risk and harm, but it notes that preclinical assays alone are "fundamentally incapable" of supporting a claim that a particular MRTP will reduce the rates of tobacco-related disease compared to another conventional product. Clinical work will therefore always be required. Further, IOM observes that research involving users of tobacco products is ethically permissible as long as the exposures in the study are not more risky than those from their current tobacco use and standard of care cessation treatment is made available. Likewise, IOM notes that, to the extent that a product has been adequately screened in preclinical work, it could safely be used in laboratory assessments of reinforcement value or self-administration.

Non-animal Testing Methods Can Be Used Exclusively to Evaluate the Health Risks Tobacco Products

On September 12, 2009, PETA submitted comments on the FDA's implementation of the Family Smoking Prevention and Tobacco Control Act that are still relevant to this draft guidance.

Tobacco industry scientists have concluded that "*in vitro* toxicology tests can be successfully used both for better understanding the biological activity of cigarette

smoke… and for guiding the development of cigarettes with reduced toxicity."[1] Currently, for example, the Canadian government's federal *Regulations Amending the Tobacco Reporting Regulations* requires that manufacturers conduct three tests to assess the toxicity of their tobacco products. All of the required tests are *in vitro*, non-animal methods – bacterial reverse mutation assay, neutral red uptake assay, and the *in vitro* micronucleus assay. These tests are widely validated and have been shown to effectively identify the mutagenicity, cytotoxicity, and clastogenicity, respectively, of whole cigarette smoke as well as individual tobacco ingredients and compounds. In addition, Belgium, Estonia, Germany, Slovakia, and the U.K. have all banned tobacco product and ingredient tests on animals.

There are also reconstructed human tissue models available for toxicity testing, including inhalation toxicity. For example, MatTek's (Ashland, Mass.) EpiAirway™ System consists of normal, human-derived tracheal/bronchial epithelial cells that have been cultured to form a pseudo-stratified, highly differentiated model closely resembling the epithelial tissue of the respiratory tract. EpiAirway tissues are grown on cell culture inserts at the air-liquid interface, allowing for gas phase exposure of volatile materials in airway inflammation and irritancy studies, as well as in inhalation toxicity studies. This system has been well characterized histologically and biochemically (cell markers) and in terms of biological response to known toxins and pharmaceuticals. Similarly the Epithelix (Plan-les-Ouates, Switzerland) MucilAir™ model has been used for many types of inhalation toxicity assessments.

Less well characterized but promising are the reconstructed human esophageal and alveolar epithelium models from SkinEthic Laboratories (Nice, France). These models use immortalized human esophageal (Kyse 510) or alveolar (A549) cells, are structurally and mechanically similar to MatTek's and also form epithelial tissue that histologically resembles cell layers of the human lung.

For oral toxicity testing, MatTek's EpiOral and EpiGingival models consist of normal, human-derived epithelial cells that allow *in vitro* study of irritation, oral pathologies, and basic oral cavity phenomena. The cells have been cultured to form multilayered, highly differentiated models of the human buccal (EpiOral) and gingival (EpiGingival) tissues. Morphologically, these tissue models closely parallel native human tissues, thus providing a useful *in vitro* means to assess irritancy, disease, and other basic oral biology phenomena. These tissue models have been extensively studied. SkinEthic also offers models of reconstructed human oral and gingival epithelium. These cell systems have been well characterized in terms of histology, biochemistry, and biological response.

At the very least, the draft guidance should support the development of new, human cell-based models of the entire human respiratory tract, especially those that model the architecture of the deep lung.

[1]Andreoli C, Gigante D, Nunziata A. A review of in vitro methods to assess the biological activity of tobacco smoke with the aim of reducing the toxicity of smoke. Toxicol in Vitro 2003: 17 (5-6):587-94.

PETA Recommendations

We support IOM's recommendation that laboratory analysis of constituents should be the first step in the evaluation of any new product. In addition to recommending that FDA convey an expected sequencing of studies, such that preclinical work is completed and submitted before clinical work commences, IOM recommends that evaluation of products *in vitro* should precede *in vivo* assays and that FDA could require that preclinical laboratory testing be completed before moving to animal or human studies. We therefore recommend that an evaluation of products *in vitro* be completed and submitted before moving to any further studies.

It is anticipated that many products will be similar to other tobacco products currently on the market, perhaps differing only in the concentration of one or more constituents already known to be harmful or potentially harmful. Laboratory analyses and evaluation *in vitro* should suffice to identify products of this type that are particularly risky or lack potential to reduce risk and harm. Development of such products need proceed no further, since any additional studies would be unlikely to restore confidence. Prior to commencement of any further studies and in accordance with Section 911(e) of the FD&C Act, FDA should make MRTP applications publicly available and request comments by interested persons. For products that are similar to other tobacco products and not particularly risky, it should be possible to select clinical exposures that are not more risky than those from study participants' current tobacco use without first conducting animal studies. Measurement of validated tobacco carcinogen and toxicant biomarkers could provide an assessment of actual exposures. For truly new products, unlike any other tobacco products currently on the market, FDA must carefully weigh the potential reduction in harm to individual tobacco users and the population as a whole against any unknown risks, for which public comment should also be requested.

Conclusion

In November 1997, the U.K. government enacted a nationwide prohibition on the use of animals for developing and testing tobacco products.[2] The Home Office stated that in making a cost-benefit analysis, it could not justify the use of animals, classifying these experiments as "morally or ethically objectionable."[3] The internationally renowned UK Nuffield Council on Bioethics reported that the Home Office, "issued a policy statement to the effect that, in making the cost-benefit assessment, these tests were no longer considered a sufficient benefit to justify any use of animals."[4]

For both scientific and ethical reasons, the continued use of animals for tobacco product testing is unjustifiable and we hope that the FDA will use its authority to ensure that only

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[2]Home Office, *Guidance on the Operation of the Animals (Scientific Procedures) Act 1986*, Chapter 5, Section 5.23, *accessed on 12 May 2008* <http://www.archive.official-documents.co.uk/document/hoc/321/321-05.htm>.
[3]Home Office, "The Cost/Benefit Assessment," Chapter 2, Annexes 1-3, Appendix F, *Report of the Animal Procedures Committee for 1997* (London: TSO) <http://www.apc.gov.uk/reference/ar97.pdf>.
[4]Nuffield Council on Bioethics (2005), "Ethics of Research Involving Animals," Chapter 13.30 <http://www.nuffieldbioethics.org/go/browseablepublications/ethicsofresearchanimals/report_406.html> accessed on: 31 Jan. 2008.

modern, human relevant and humane non-animal testing methods will be used by tobacco product manufacturers to assess the risks of their products and fulfill data submission requirements. We ask that FDA convene a meeting with scientists from animal protection organizations in order to establish specific guidance to industry to ensure that animals are not used in support of MRTP applications. .

Thank you for your attention to these comments. I can be reached at 757-622-7382, ext. 8001 or via email at JosephM@peta.org.

Sincerely,

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